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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/235,986 01/22/99 HENDRICKSON

W 58323/JPW/PT

EXAMINER

HM12/0531

JOHN P WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF AMERICAS
NEW YORK NY 10036

LUNDGREN, J

ART UNIT

PAPER NUMBER

1631

DATE MAILED:

05/31/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/235,986

Applicant(s)

HENDRICKSON ET AL.

Examiner

Jeffrey S. Lundgren

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- 1) ☒ Responsive to communication(s) filed on 10 April 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
 2. ☐ received in Application No. (Series Code / Serial Number) _____.
 3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

DETAILED ACTION

Oath/Declaration

1. The objection to the oath or declaration in the Office action mailed on October 6, 1999 (paper No. 5), has been overcome by a substitute oath or declaration received on April 19, 2000 (paper No. 7).

Specification

2. The objection to the abstract in the Office action mailed on October 6, 1999 (paper No. 5), has been overcome by the amendment received on April 19, 2000 (paper No. 7).

Claim Rejections - 35 USC § 112

3. Applicant has overcome the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph, in the Office action mailed on October 6, 1999 (paper No. 5), by deleting the phrase "all known structural information" in the amendment received on April 19, 2000 (paper No. 7).

4. Applicant has overcome the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph, in the Office action mailed on October 6, 1999 (paper No. 5), by deleting the phrase "an ensemble of all known structures is used to further advance an

effectiveness of said bioinformatics tools” in the amendment received on April 19, 2000 (paper No. 7).

Claim Rejections - 35 USC § 103

5. Applicant has overcome the rejection of claims 1-12 under 35 U.S.C. 103(a) as being obvious in view of Cohen et al. (U.S. Patent No. 5,878,373, March 2, 1999) in the Office action mailed on October 6, 1999 (paper No. 5), by means of amendment received on April 19, 2000 (paper No. 7). Cohen et al., disclose a system and a method for predicting the protein fold of a target amino acid sequence (where the experimental 3D structure is undetermined) with a catalogued protein structure.

6. Applicant has overcome the rejection of claims 1-12 under 35 U.S.C. 103(a) as being obvious in view of Eisenberg et al. (U.S. Patent No. 5,878,373, March 2, 1999) in view of Kreisberg et al. (Protein Science 4, 2405-2410, **1995**), in the Office action mailed on October 6, 1999 (paper No. 5), by means of amendment received on April 19, 2000 (paper No. 7). Eisenberg et al., disclose a computer assisted method for identifying protein sequences that fold into a known three-dimensional structure through attacking the “inverse protein folding” problem.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 1, 3, 5-7, 9, and 11-12, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachar et al. (Protein Engineering 6, 279-288, 1993), in view of Hendrickson et al. (The EMBO Journal 9, 1665-1672, 1990).

Claims 1, 3, 5-7, 9, and 11-12, are drawn to a system and process for determining experimentally a plurality of three-dimensional atomic structures, each associated with a corresponding protein, first a protein database of sequence information and known structural and functional information which is systematically organized, must be established for integration with at least one bioinformatics tool using the structural and functional information to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences. Afterwards, the analysis of the target protein using sequence of the information corresponding to other family members of the database and information corresponding to other known three-dimensional structures which is stored in the database, with means for refining the model for functional motifs, and means for defining at least one class of compound predicted to have binding potency using the active site information.

Bachar et al., teach a method/system for protein classification, wherein an experimentally-derived, three-dimensional structure of a target protein can be classified by assignment to a cluster set of structurally similar, three-dimensional representation of proteins in an organized database. The design and organization of the database consists of three major steps: 1) finding relatively small subset of the structures that form an initial match; 2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues. These steps are further comprised of sub-steps detailed in the disclosure (pages 280-283). As a result of organizing a database and developing a means to utilize the database for similarity comparisons/clustering, one can determine a surface motif in a target protein, one can determine an activity of a given compound to the target protein, and one can objectively determine a number of chemical or biological properties of the target protein (see *Conclusions*).

Although Bachar et al., utilize data which represent the three-dimensional structures of proteins, the investigators do not disclose a means for preparing proteins, a means of preparing protein crystal for analysis, a means of three-dimensional analysis, or any peripheral mean for data acquisition.

Hendrickson et al., teach a system and process for incorporating selenomethionine (as a replacement for methionine) into recombinant proteins produced from plasmids in *E. coli.*, which are crystallized and analyzed by multiwavelength anomalous diffraction (MAD) as a means for producing a three-dimensional representation of a target protein. Their method provides the advantages

over conventional x-ray techniques for elucidating three-dimensional protein structures, in that MAD utilizes the scattering effects of resonance between x-rays and bound atomic orbitals, it is perfectly isomorphic, allows for data sampling from a single crystal, and the analysis is algebraically exact (see *Introduction*).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the selenomethionyl protein expression technique for MAD analysis with the three-dimensional, protein structure classification method/process taught by Bachar et al., because Hendrickson et al., teach the aforementioned advantages of using their method/system for recovering data sets representing the three-dimensional structure of proteins over conventional x-ray crystallographic methods. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

9. Claims 4 and 10, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachar et al., and Hendrickson et al., as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Lima et al. (Structure 5, 763-774, **1997**).

Claims 4 and 10, are drawn to the system and process of claims 1 and 7, respectively, wherein the synchrotron storage ring has undulator beamlines for use with MAD.

Neither Bachar et al., nor Hendrickson et al., teach a synchrotron storage ring which has undulator beamlines for use with MAD.

Lima et al., teach using an undulator beamline x-ray source, with MAD because of the high output levels, with narrow, tunable, harmonic peaks (see *Results and Discussion*).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the undulator beamline x-ray source, in place of the synchrotron device as taught by Hendrickson et al., because Lima et demonstrate of a high output x-ray source, with narrow, tunable, harmonic peaks. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

10. Claims 2 and 8, are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Craig et al., (U.S. Patent No. 5,525,198, June 11, 1996).

Claims 2 and 8, are drawn to the system and process of claims 1 and 7, respectively, wherein a cryogenic freezing means is used to freeze the target protein crystal.

Neither Bachar et al., or Hendrickson et al., disclose the use of crogenic freezing means to freeze the target protein crystal.

Craig et al., teach the cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to x-ray sources (column 5, lines 3-18).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a means for the cryogenic cooling of the target protein crystal, with the system/process of Bachar et al., in view of Hendrickson et al., as Craig

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et al., teach that cryogenic cooling preserves crystals during x-ray sampling. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

Conclusion

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeffrey S. Lundgren whose telephone number is (703) 306-3221. The Examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM (EST), and alternating Fridays from 8:00 AM to 4:30 PM (EST).

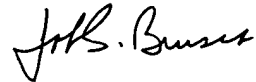
If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Michael Woodward, can be reached at (703) 308-4028.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

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Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1631 using (703) 308-0294. Please notify the Examiner of incoming facsimiles prior to sending papers to the aforementioned fax number. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Jeffrey S. Lundgren, Ph.D.

A handwritten signature in black ink, appearing to read "John S. Brusca".

JOHN S. BRUSCA, PH.D.
PRIMARY EXAMINER